PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerc
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 08 March 2001 (08.03.01)	
International application No.: PCT/EP99/06348	Applicant's or agent's file reference: 20-99-0021
International filing date: 28 August 1999 (28.08.99)	Priority date:
Applicant: FISCHER, Bernhard	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

19 September 2000 (19.09.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer: J. Zahra Telephone No.: (41-22) 338.83.38

F ENT COOPERATION TRE

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

MEYER, Michael
Philips Corporate Intellectual
Property Gmgh
Habsburgerallee 11
52064 Aachen
ALLEMAGNE

Date of mailing (day/month/year)
01 November 2001 (01.11.01)

Applicant's or agent's file reference
20-99-0021

IMPORTANT NOTIFICATION

International application No.
PCT/EP99/06348

International filing date (day/month/year)
28 August 1999 (28.08.99)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address

VOLMER, Georg
c/o Philips Corporate Intellectual
Property
Habsburgerallee 11
52064 Aachen
Germany

State of Nationality

State of Residence

Telephone No.
0241 70 40 32P

Facsimile No.
0241 70 40 70

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

MEYER, Michael
Philips Corporate Intellectual
Property Gmgh
Habsburgerallee 11
52064 Aachen
Germany

State of Nationality

State of Residence

Telephone No.
0241 70 40 32P

Facsimile No.
0241 70 40 70

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☒ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Catherine MASSETTI

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994) 004420607

P ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

BARTH, Daniel
Hewlett-Packard GmbH
Europäische Patent- und Lizenzabt.
Herrenberger Strasse 140
D-71034 Böblingen
ALLEMAGNE

Date of mailing (day/month/year)	
24 April 2001 (24.04.01)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
20-99-0021	
International application No.	**International filing date** (day/month/year)
PCT/EP99/06348	28 August 1999 (28.08.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
HEWLETT-PACKARD COMPANY Corporate Offices 3000 Hanover Street Palo Alto, CA 94304 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
AGILENT TECHNOLOGIES, INC. 395 page Mill Road Palo Alto, CA 94303 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer F. Baechler
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

F ENT COOPERATION TREA . .

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

VOLMER, Georg
c/o Philips Corporate Intellectual Property
Habsburgerallee 11
52064 Aachen
ALLEMAGNE

Date of mailing (day/month/year)
08 October 2001 (08.10.01)

Applicant's or agent's file reference
20-99-0021

IMPORTANT NOTIFICATION

International application No.
PCT/EP99/06348

International filing date (day/month/year)
28 August 1999 (28.08.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
AGILENT TECHNOLOGIES, INC.
395 page Mill Road
Palo Alto, CA 94303
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [X] the nationality [X] the residence

Name and Address
PHILIPS CORPORATE INTELLECTUAL PROPERTY GMGH
Habsburgerallee 11
52064 Aachen
Germany

State of Nationality: DE
State of Residence: DE
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Catherine MASSETTI
Telephone No.: (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/06348

Box I Observations wher certain claims were f und unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 6-8
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
20-99-0021		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/ 06348	28/08/1999	
Applicant		
HEWLETT-PACKARD COMPANY et. al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 3

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
20-99-0021		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/06348	28/08/1999	28/08/1999
International Patent Classification (IPC) or national classification and IPC A61M16/01		
Applicant PHILIPS CORPORATE INTELLECTUAL PROPERTY GMBH et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19/09/2000	30.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Rosenblatt, T Telephone No. +49 89 2399 8732

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/06348

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4784486 A	15-11-1988	AT 96227 T	15-11-1993
		AU 612732 B	18-07-1991
		AU 2607888 A	02-05-1989
		CA 1323205 A	19-10-1993
		DE 3885104 D	25-11-1993
		DE 3885104 T	04-08-1994
		EP 0380580 A	08-08-1990
		JP 7086462 B	20-09-1995
		JP 3501518 T	04-04-1991
		KR 9514941 B	18-12-1995
		WO 8903515 A	20-04-1989
DE 2723939 A	07-12-1978	NONE	
US 5733505 A	31-03-1998	NONE	
EP 0557658 A	01-09-1993	DE 69219580 D	12-06-1997
		DE 69219580 T	11-09-1997
		JP 6242002 A	02-09-1994
		US 5450193 A	12-09-1995
EP 0814333 A	29-12-1997	US 5929981 A	27-07-1999
		CA 2204587 A	18-12-1997
		JP 10062348 A	06-03-1998

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/06348

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M16/01 A61M16/10 G01N21/65

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 784 486 A (VAN WAGENEN RICHARD A ET AL) 15 November 1988 (1988-11-15) column 4, line 47 - line 50 column 5, line 6 - line 10 column 10, line 12 - line 16 column 17, line 6 - line 8 column 17, line 46 - line 47 column 20, line 67 -column 21, line 4 ---	1-5
X	DE 27 23 939 A (ALBRECHT HANS JOERG) 7 December 1978 (1978-12-07) page 7, line 14 - line 18 page 9, line 12 - line 14 page 11, paragraph 2 -page 12, paragraph 1 page 17, line 29 --- -/--	1-5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 April 2000	26/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lakkis, A

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 733 505 A (HELFMAN WILLIAM B ET AL) 31 March 1998 (1998-03-31) column 1, line 54 - line 57 column 3, line 1 - line 5 column 5, line 13 - line 17 column 6, line 29 - line 43	1,3
A	EP 0 557 658 A (HEWLETT PACKARD CO) 1 September 1993 (1993-09-01) column 3, line 7 - line 14	1-5
A	EP 0 814 333 A (OHMEDA INC) 29 December 1997 (1997-12-29) column 1, line 25 - line 32	1-5

1

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/06348

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-10 as originally filed

Claims, No.:

1-8 as originally filed

Drawings, sheets:

1/1 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 6-8.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 6-8.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims

	No:	Claims	1-5
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-5
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re It m V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following document:

   D1 = US-A-4 784 486.

2. The document D1 is regarded as being the closest prior art to the subject-matter of claim 1, and insofar as this claim can be understood (see Section VIII), this document shows the following features thereof (the references in parentheses applying to this document):

   a system suitable for avoiding poisoning effects during anesthesia (col. 1, lines 14-17; col. 5, lines 1-15) comprising:
   - determining means (Fig. 2) suitable for determining the quantitative amount of an anesthetic agent degradation product in an anesthetic gas mixture (col. 17, lines 6 to 8),
   - alarm means suitable for providing an alarm when the determined quantitative amount of the anesthetic agent degradation product in the anesthetic gas mixture exceeds a given threshold (col. 20, lines 26-46).

   Since all the features of claim 1 are known, this claim lacks novelty (Art. 33(2) PCT) with respect to D1. Although the intended use is not disclosed in D1, the system of D1 is however **suitable** for this use, since it possesses the necessary technical features.

3. Dependent claims 2 to 4 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty, the reasons being as follows:

3.1 D1 shows measuring means suitable for measuring a Raman spectrum of the gas mixture and also a processing unit suitable for the function indicated in claim 2, so that also claim 2 lacks novelty in view of D1.

3.2 Claims 3 and 4 do not define any further technical feature of the system (see Section VIII below), so that these claims also lack novelty in view of D1.

It is appreciated that D1 does not disclose the monitoring of CHF_3. However even if the subject-matter of claim 4 could be clarified, by clearly formulating a technical feature of the system, in order to eliminate the below mentioned clarity objection it is questionable if such a claim, which would then probably be new with respect to D1, could meet the requirements of inventive activity (Art. 33(3) PCT), since it appears to be a simple alternative to the already known CO-monitoring.

4. Independent claim 5 is a combination of the features defined in claims 1 and 2 and hence does not meet the requirement of novelty (Art. 33(2) PCT).

5. The system according to claims 1 to 5 may be industrially manufactured and commercialised, so that these claims meet the requirements of Art. 33(4) PCT.

Re Item VII

Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.

2. Independent claims should be in the two-part form in accordance with Rule 6.3(b) PCT, which in the present case would be appropriate, with those features known in combination from the prior art (document D1) being placed in the preamble (Rule 6.3(b)(i) PCT) and with the remaining features being included in the characterising part (Rule 6.3(b)(ii) PCT).

Re Item VIII

Certain observations on the international application

1. Claims 1 to 5 lack clarity within the meaning of Art. 6 PCT, in that the functional statements (for avoiding..., for determining..., for providing...) made in connection with the definition of the different "means" do not allow to draw a clear distinction

in terms of technical features over the prior art. The functional statements are interpreted according to the PCT Guidelines, Section IV, III-4.8a and IV-7.6 as implying only the suitability of the respective means. Consequently, any feature known from the prior art and suitable to perform the desired function takes away the novelty of the corresponding feature in the claim. This objection also holds with respect to the object of claim 1, which is **a system for avoiding poisoning effects...** Only an intended use is defined, which does however not allow to clearly distinguish the subject-matter of claim 1 over the prior art.

2. The claims do further not comply with Art. 6 PCT, in that they are not concise in view of claims 1 to 4 and 5, where claim 5 defines only a combination of the features of claims 1 to 4.

3. Claims 3 and 4 are not clear (Art. 6 PCT), in that they do not define actual features of the system, since an anesthetic agent degradation product to be monitored by the system cannot be a feature of the system itself. The claims are considered void of additional technical features.

4. The term **preferably** used in claims 4, 5, 6 does not impose a limitation to the subject-matter of the respective claims by the features following on it (PCT-Guidelines Section IV, III-4.6).

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 March 2001 (08.03.2001)

PCT

(10) International Publication Number
WO 01/15762 A1

(51) International Patent Classification[7]: A61M 16/01, 16/10, G01N 21/65

(21) International Application Number: PCT/EP99/06348

(22) International Filing Date: 28 August 1999 (28.08.1999)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant *(for all designated States except US)*: **HEWLETT-PACKARD COMPANY** [US/US]; Corporate Offices, 3000 Hanover Street, Palo Alto, CA 94304 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **FISCHER, Bernhard** [DE/DE]; Trochtelfinger Weg 12, D-71229 Leonberg (DE).

(74) Agent: **BARTH, Daniel**; Hewlett-Packard GmbH, Europäische Patent- und Lizenzabt., Herrenberger Strasse 140, D-71034 Böblingen (DE).

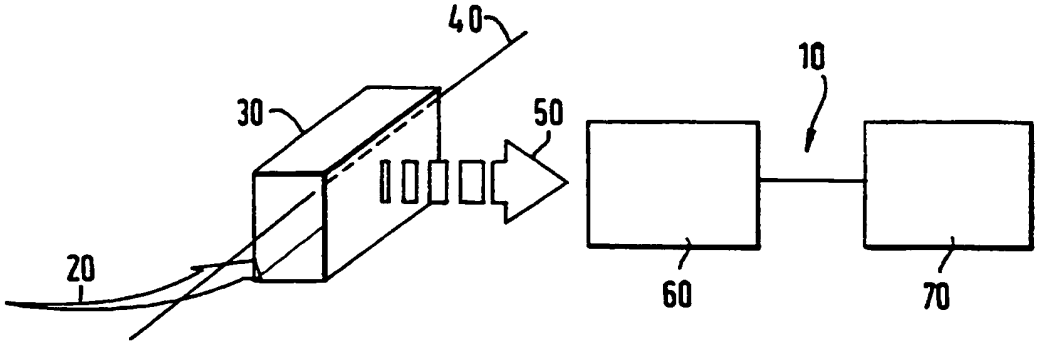
(81) Designated States *(national)*: JP, US.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: AVOIDANCE OF POISONING EFFECTS DURING ANESTHESIA



(57) Abstract: For avoiding poisoning effects during anesthesia, the quantitative amount of an anesthetic agent degradation product, preferably carbon monoxide CO and/or trifluoromethane CHF_3, in an anesthetic gas mixture is determined. When the determined quantitative amount of the anesthetic agent degradation product in the anesthetic gas mixture exceeds a given threshold, an alarm is provided. This is preferably accomplished by measuring a Raman spectrum of the gas mixture, and determining the quantitative amount of the anesthetic agent degradation product in the gas mixture by comparing the measured Raman spectrum with a reference spectrum of the anesthetic agent degradation product.

WO 01/15762 A1

AVOIDANCE OF POISONING EFFECTS DURING ANESTHESIA

BACKGROUND OF THE INVENTION

The present invention relates to poisoning effects during anesthesia.

During anesthesia with one of the agents desflurane, isoflurane or enflurane, it has been observed that patients can accidentally become exposed to carbon monoxide, CO, thus leading to an inadvertent CO-poisoning of the patient. Peter B. Berry et al. in *"Severe Carbon Monoxide Poisoning during Desflurane Anesthesia"*, Anesthesiology V 90, No. 2, Feb 1999, p. 613 report 36% COHb as highest CO level in blood due to this effect, i.e. 36% of hemoglobin loaded with CO (instead of oxygen) after only 15 min of anesthesia time with desflurane. A degradation of the anesthetic agent used in conjunction with Baralime or Sodalime, generally used as absorber material for CO_2 in circle breathing systems, has been identified as origin of this exposure. It has been found that degradation of the agent occurs under a condition that the CO_2 absorber material is too dry. Carbon monoxide, CO, has been identified as one of the degradation products.

Usually, the accidental CO exposure goes undetected, because CO is not identified or measured by the commercially available medical gas monitors. Although clinicians are aware of the potential problem, its early recognition and immediate remedy requires experience and a thorough knowledge of the behavior of the monitoring equipment used. In the above case, described by Peter B. Berry et al., the detection occurred through a sequence of strange observations, 1st the oxygen saturation of the patient decreased to 93% in spite of a fresh gas flow with 100% oxygen, 2nd the gas analyzer being set to automatic agent identification mode suddenly switched to „enflurane" in spite of the desflurane used. Only then, the

clinicians suspected CO poisoning resulting from desiccation of the CO_2 absorber. A blood analysis for COHb confirmed that suspicion.

The intoxication by CO occurs through the strong binding of this molecule to hemoglobin in competition to the binding of oxygen. The affinity of hemoglobin to CO, however, is 300 times stronger than to oxygen. Therefore, it is a question of the dosage of CO that determines the COHb level in blood. Harrison N. et al. in Anesthesia, Vol. 51, p 1037-1040 (1996) notes that a CO level of 0.1% for 1 h gives a COHb level of approximately 30% and evidence of moderate to severe toxicity. In the case reported by Peter B. Berry et al., the measured COHb level was 36% after 15 min of anesthesia time. It can be concluded that the CO concentration in the inhaled gas stream in his reported case must have been of the order of 0.5%.

Gas analyzers normally applied in anesthetic environments are based on gas detection by absorption measurements. Primarily, the infrared (IR) spectral region is used. The unusual behavior of the gas analyzer in the above reported case was explained by the similarity of the infrared absorption spectrum between another degradation product trifluoromethane, CHF_3, and enflurane, thus leading to the erroneous identification of the anesthetic agent.

It has been speculated by Harvey J. Woehlck in "*Severe Intraoperative CO Poisoning*", Anesthesiology V 90, No. 2, Feb 1999, p. 353 (Editorial), that a very large number of patients are at risk to be exposed to undetected CO levels, in particular the first cases in the morning or cases on anesthesia machines that are infrequently used. Also, the use of a high flow of fresh (dry) gas enhances the likelihood that the CO_2 absorber material becomes desiccated and starts to break down the agent molecules.

The complete avoidance of the described problem would require strict discipline

with the renewal/exchange routine of the CO_2 absorber material (cf. Harvey J. Woehlck et al., Reduction in the Incidence of Carbon Monoxide Exposures in Humans Undergoing General Anesthesia, Anesthesiology V87, No 2, Aug 1997, p. 228). However, since this strict discipline with the renewal/exchange routine appears to be hardly feasible, an early and unambiguous identification of CO gas would be desirable. The gas monitors presently used in clinics, however, are not capable of detecting CO and react only indefinitely to its presence in the breathing gas mixture and mostly provide erroneous information to the user.

SUMMARY OF THE INVENTION

It is therefore an object of the invention to avoid poisoning effects during anesthesia. The object is solved by the independent claims. Preferred embodiments are shown by the dependent claims.

According to the invention, the CO concentration in a respiration gas is directly and/or indirectly measured in a substantially continuous monitoring process. An alarm will be provided when the monitored concentration exceeds one or more given threshold values. Thus, a timely warning can be issued so that the clinical personnel can replace the CO_2 absorber material before any harm will be done to the patient.

An indirect monitoring of the CO concentration in a respiration gas is applied by measuring a by-product of the anesthetic agent degradation process other than CO. Preferably, a by-product is selected which is absorbed in the body to a much lower degree than CO and thus easier to detect than CO. The by-product is thus employed as an indicator for the presence of CO. Preferably, trifluoromethane, CHF_3, is employed as such an indicator. CHF_3 can be detected using Raman or IR spectroscopy.

It has been shown that the physiologically relatively harmless CHF_3 provides an excellent indicator for the presence of the dangerous CO. Since CO is virtually "sucked" by the lungs into the blood, the CO concentration in the respiration circle normally remains relatively low. The concentration of CHF_3, in contrast thereto, will be accumulated in the respiration circle, because CHF_3 is normally bound or absorbed in the body to a much lower degree than CO. Therefore, the concentration of CHF_3 in the respiration circle will be normally much higher than the concentration of CO and is thus much easier to detect.

A direct monitoring of the CO concentration in a respiration gas is applied using Raman spectroscopy for directly detecting the presence of anesthetic agent degradation products in a respiration gas such as CO and/or any other degradation product, like CHF3, which can be employed as an indicator for the presence of CO.

The invention preferably applies **Raman scattering** for gas analyzing purposes. Gas detection, in general, is accomplished either by using optical absorption or by scattering of light. Scattering of light occurs as a consequence of the electronic polarizability of the electron cloud around atoms and molecules. Most incident photons are scattered by the sample with no change in frequency in a process known as Rayleigh scattering. Rayleigh scattering occurs from molecular as well as atomic species. However, with a small probability the scattered photons have frequencies f_0 +/- f_1, where f_0 is the frequency of the incident photon and f_1 is the frequency of a molecular vibration. This process is called Raman scattering. The modification of the scattered photons results from the incident photons either gaining energy from or losing energy to the vibrational or rotational motion of the molecule. Since complex molecules exist in a number of different rotational and vibrational states (depending on the temperature), many different values of f_1 are possible. Consequently, the Raman spectrum of a ***Raman-active gas*** will consist of a large number of scattered lines. Simple diatomic molecules like oxygen, O_2, or

nitrogen, N_2, have just one Raman line.

To enhance the observation of the radiation at f_0 +/- f_1, the scattered radiation is observed perpendicularly to the incident beam. To provide high intensity incident radiation and to enable the observation of lines where f_1 is small (due to rotational changes), the source of a Raman spectrometer is normally chosen as a monochromatic visible laser. The scattered radiation can then be analyzed by use of a scanning optical monochromator with a photomultiplier tube or another suitable photo detector.

Gas analyzers employing Raman spectroscopy can be calibrated to various Raman-active gases. The spectral „fingerprint" of Raman-active gases can be used to identify constituents of even very complex gas mixtures, and the relative intensity of the spectral contributions by each member gas is used to quantify the gases.

In a preferred embodiment of the invention, a gas analyzer employing Raman spectroscopy is calibrated to one or more anesthetic agent degradation products such as CHF_3, CO and/or other species of interest, normally in addition to the usual respiratory and anesthetic gases. Calibration herein means that a reference spectrum of the respective Raman-active gas is stored and will be used for detecting the respective Raman-active gas. As soon as the Raman gas monitor detects amounts of unwanted species exceeding pre-given threshold values, a warning sign will be generated thus alerting e.g. the clinician and giving direct and clear information about the origin and nature of the problem.

In one embodiment, a (direct) CO detection and monitoring is applied for generating a warning signal against impending CO poisoning. In another embodiment, the detection of any other degradation product like the CHF_3 compound is employed. CHF_3 gives a very strong Raman signal, and it has been verified that the lower

detection limit is well below 0.1%. CO is strongly bound to hemoglobin (the affinity of Hb to CO is 300 times larger than to oxygen) such that inhaled gas gets depleted from CO very effectively, while the CHF_3 stays in the breathing circuit and rapidly enriches to higher concentrations. Therefore, CHF_3 represents a fairly good indicator gas for CO presence.

In a preferred embodiment of the invention, a Raman gas analyzer is employed using a laser source in the visible spectral region to excite the Raman spectrum. The Raman gas analyzer might further be equipped with a spectrometer to measure Raman lines in a spectral range of preferably about 200 nm from the excitation wavelength. This gas analyzer can be calibrated for Raman-active gases by exposing the Raman measurement cell to a pure sample (or diluted mixture) containing this gas and recording the respective Raman spectrum as a calibration spectrum. This way, the analyzer can be calibrated for CO and/or CHF_3, also in addition to the other respiratory and anesthetic gases of interest to the user.

An alarming algorithm is implemented preferably triggered by the detection of CO and/or CHF_3 in the breathing gas stream during clinical use. This alarm indicates to a user to check the CO_2 absorber and to exchange it against fresh material immediately in order to avoid CO poisoning of the patient.

The gas monitor in accordance with the present invention provides an early warning capability against CO poisoning and permits that accidental CO poisoning by the described degradation process can be reliably avoided. Although there is great uncertainty in the medical literature about the true morbidity from interoperative CO poisoning and about the resulting economic damage, it is well known that even moderate levels of a few percentage of COHb in patients undergoing cardiac, cranial, or spinal surgery may cause severe oxygen deficiencies. Prolonged oxygen deficiency leads to neurological disorders.

A further possibility for determining anesthetic agent degradation products is to use infrared absorption spectroscopy for the detection of CO and/or CHF_3. However, the larger widths and overlaps in IR absorption bands of the species of interest render the identification task to be fairly complex. A currently available medical gas analyzer would have to be fitted with additional optical filters, and the algorithms would have to be changed accordingly. The effort for both is very costly.

BRIEF DESCRIPTION OF THE DRAWINGS

Other objects and many of the attendant advantages of the present invention will be readily appreciated and become better understood by reference to the following detailed description when considering in connection with the accompanied drawings. Features that are substantially or functionally equal or similar will be referred to with the same reference sign(s).

Fig. 1 depicts the schematic view of a gas monitor 10 according to the invention, and

Fig. 2 shows an example of a measurement of a composition of a gas mixture with a number of gas constituents.

DETAILED DESCRIPTION OF THE INVENTION

Fig. 1 depicts the schematic view of a gas monitor 10 according to the invention. A gas flow 20 with a gas mixture such as a respiration gas is directed through a sample cell 30. An incident light beam 40, e.g. from a laser source, is scattered in the sample cell 30 and a scattering light 50 is received by a spectrograph 60. The spectrograph 60 is further coupled to a processing unit 70 for determining the composition of the gas mixture in the gas flow 20.

The processing unit 70 is preferably further connected (not shown) to the source of

the light beam 40 for receiving information about the light beam 40, such as the intensity. The processing unit 70 is preferably further coupled to a (not shown) pressure determining means and a temperature sensor within the sample cell 30 for receiving information about the pressure and temperature therein.

In a first step, the spectrograph 60 of the gas monitor 10 measures the Raman spectrum of the gas mixture. In a second step, the processing unit 70 then determines the quantitative amount of one or more anesthetic agent degradation products in the gas mixture of the gas flow 20 by comparing the measured Raman spectrum with stored reference spectra of anesthetic agent degradation products. Each reference spectrum generally represents the Raman spectrum for the pure gas component, determined under known conditions, e.g. a known condition of pressure and/or temperature within the sample cell 30 and of the intensity of the incident light beam 40. Accordingly, reference spectra can be applied already representing a defined gas mixture. The proportion of the measured spectrum to each reference spectrum provides a direct measure of the proportion of the individual gas component (represented by the reference spectrum) in the gas mixture.

The assignment of the peak(s) in the measured spectrum to the individual gas component(s) can be done as known in the art, e.g. by comparing the wavelength(s) of the peak(s) with the wavelength(s) of the reference spectrum/spectra of the individual gas component(s).

The comparison of the measured Raman spectra with the reference Raman spectra is preferably accomplished by determining the ratio of the amplitudes (intensities) for each wavelength channel of the spectrograph. However, other comparison methods e.g. by means of the peak area or the like can be applied accordingly.

In case that a certain individual gas component reveals more than one Raman line, all lines are preferably attenuated substantially evenly, so that, for the purpose of the invention, it is normally sufficient to evaluate only one Raman line for each gas component for determining the proportion of the individual gas component in the gas mixture.

The reference spectra comprising the wavelength positions and intensities are preferably determined by previous measurements and can be stored e.g. in a calibration matrix.

In case that the actual measuring conditions deviate from the measuring conditions of the reference spectra, the measured spectra have to be corrected, e.g. for the effects of pressure, temperature, and light intensity changes, using well-known algorithms.

Fig. 2 shows an example of a measurement of a composition of a gas mixture with a number of gas constituents. The spectrograph 60 measures a Raman spectrum 100 of the gas mixture. The wavelength position and intensities of a plurality of Raman lines are stored in a calibration matrix 110 with a plurality of individual reference spectra 110A...110Z for several gas constituents.

The measured spectrum 100 of the gas mixture is compared with the respective reference spectra 110A, 110B of the calibration matrix 110. The proportions of the peak levels from the reference spectra 110A, 110B, and 110Z to the measured spectrum 100 provides a direct measure for the proportions of the individual components in the gas mixture. In the example of Fig. 2, the wavelength and characteristics of the measured peaks refer to N_2, O_2, CHF_3, and CO. In this example, the peak N_2 shall represents 77% of the reference peak for N_2 in the reference spectrum 110A, the peak O_2 represents 21% of the reference peak for O_2

in the reference spectrum 110B, and both CHF_3 peaks (to the very left and right in the spectrum 100) represents 1% of the reference peak for CHF_3 in the reference spectrum 110Z. The peak CO represents about 0.5% of the reference peak for CO (not shown in 110). Accordingly, the gas composition of the measured spectrum 100 is: 77% of N_2, 21% of O_2, 1% of CHF_3, and about 0.5% of CO.

When the determined quantitative amount of one or more of the anesthetic agent degradation products in the gas mixture exceeds given threshold values for each of the degradation products, an alarm will given in a third step. The determination of reasonable threshold values for the detection of the degradation products is of course dependent on the sensitivity of the specific embodiment of the measurement system. Since one dangerous aspect of CO poisoning is the dose (the dose being the concentration multiplied by the exposure time) deposited in the blood hemoglobin, the optimization of the threshold values should preferably take into account both the detection limits for the degradation products as well as the system's integration time associated with those detection limits. On one hand, it is desirable to have threshold values as low as possible in order to generate a warning as early as possible, but, on the other hand, false-positive alarms triggered in an overly sensitive system are to be avoided, too. In a preferred embodiment, threshold values of 0.5% for CHF_3 and/or 0.2% for CO have been proved satisfactory. If more than one degradation product are monitored simultaneously a further increase in reliability of the alarm can be obtained from correlating the detection of these products at concentrations above the set threshold values.

In another preferred embodiment, only one of the anesthetic agent degradation products is used for monitoring possible CO-poisoning of patients in anesthesia. Preferably, only CHF_3 will be monitored since CHF3 provides a sufficiently strong Raman signal and it has been verified that the lower detection limit is well below 0.1%.

CLAIMS:

1. A system (10) for avoiding poisoning effects during anesthesia, comprising:

determining means (60, 70) for determining the quantitative amount of an anesthetic agent degradation product in an anesthetic gas mixture, and

alarm means for providing an alarm when the determined quantitative amount of the anesthetic agent degradation product in the anesthetic gas mixture exceeds a given threshold.

2. The system (10) of claim 1, wherein the determining means (60, 70) comprises:

measuring means (60) for measuring a Raman spectrum of the gas mixture, and

a processing unit (70) for determining the quantitative amount of the anesthetic agent degradation product in the gas mixture by comparing the measured Raman spectrum with a reference spectrum of the anesthetic agent degradation product.

3. The system (10) of claim 1 or 2, wherein the anesthetic agent degradation product is carbon monoxide CO.

4. The system (10) according to any one of the above claims, wherein the anesthetic agent degradation product is trifluoromethane, CHF_3, preferably as an indicator for the presence of CO in the gas mixture.

5. A system (10) for avoiding CO poisoning effects during anesthesia caused by anesthetic agent degradation products in a gas mixture such as a respiration gas, comprising:

means (60) for measuring a Raman spectrum of the gas mixture,

a processing unit (70) for determining the quantitative amount of at least one of the anesthetic agent degradation products, preferably CHF_3 and/or CO, in the gas mixture by comparing the measured Raman spectrum with a reference spectrum of the at least one anesthetic agent degradation products, and

means for providing an alarm when the determined quantitative amount of the anesthetic agent degradation product in the gas mixture exceeds a given threshold.

6. A method for avoiding poisoning effects during anesthesia, comprising the steps of:

(a) determining the quantitative amount of an anesthetic agent degradation product, preferably carbon monoxide CO and/or trifluoromethane CHF_3, in an anesthetic gas mixture, and

(b) providing an alarm when the determined quantitative amount of the anesthetic agent degradation product in the anesthetic gas mixture exceeds a given threshold.

7. The method of claim 6, wherein the step (b) comprises the steps of:

(c) measuring a Raman spectrum of the gas mixture, and

(d) determining the quantitative amount of the anesthetic agent degradation product in the gas mixture by comparing the measured Raman spectrum with a reference spectrum of the anesthetic agent degradation product.

8. Use of a Raman spectrometer (60, 70) for determining the quantitative amount

of an anesthetic agent degradation product in a gas mixture.

FIG. 1

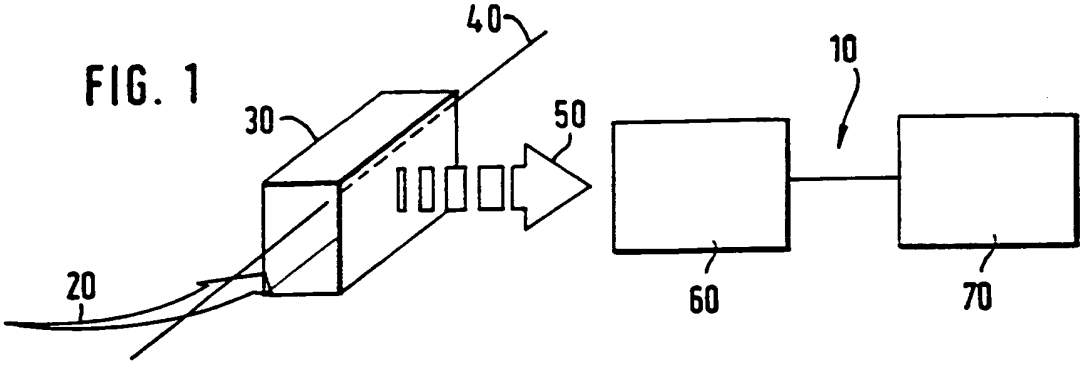
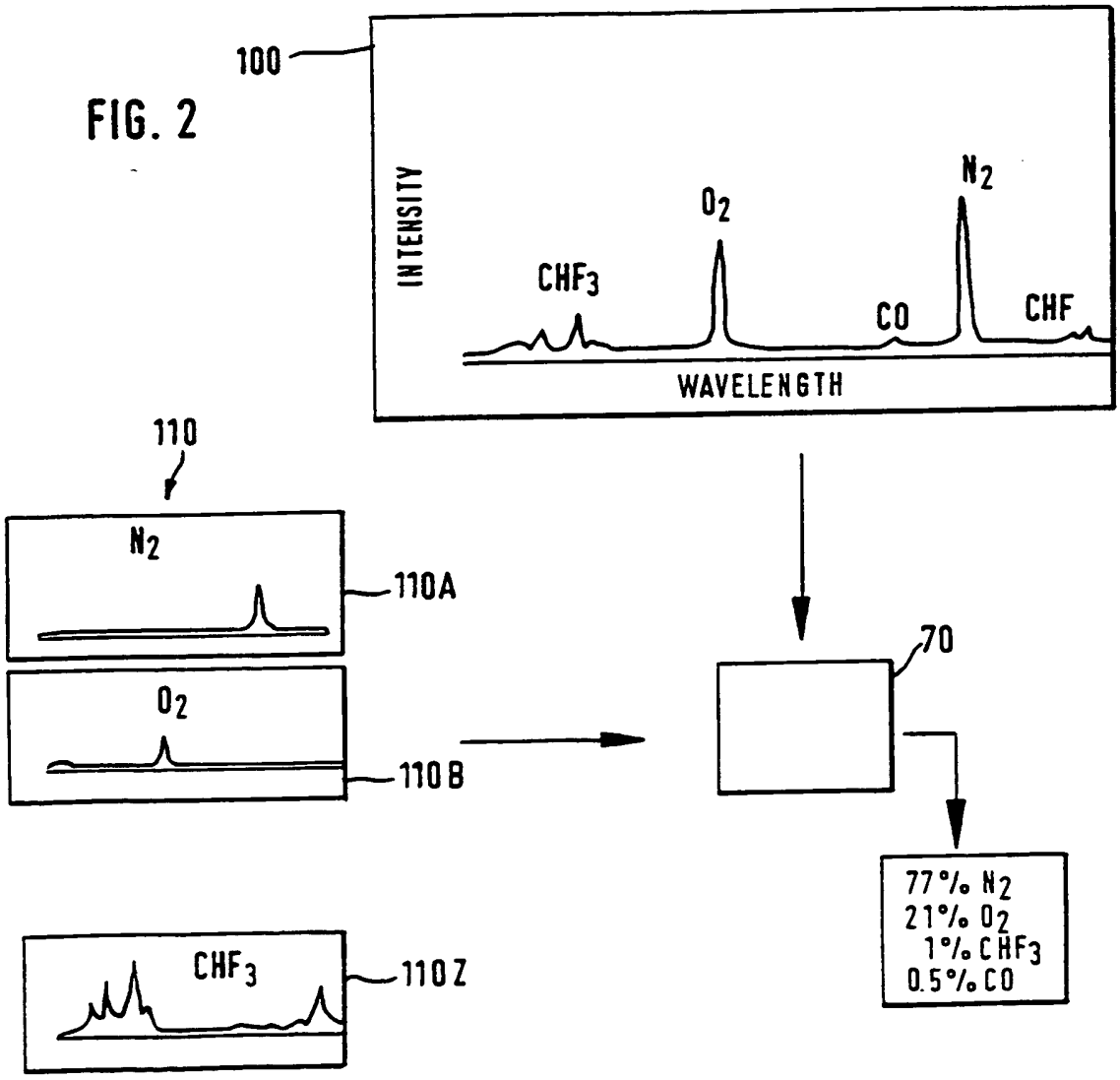

40
10
30
50
20
60
70

FIG. 2


100
INTENSITY
N_2
O_2
CHF_3
CO
CHF
WAVELENGTH
110
N_2
110A
O_2
110B
70
77% N_2
21% O_2
1% CHF_3
0.5% CO
CHF_3
110Z